

REMARKS

Applicant requests a telephonic interview with the examiner, to be conducted before the examiner acts upon this amendment. Depending on the outcome of the interview, Applicant may be willing to file a supplemental amendment to further narrow the issues in this case. The examiner should call Counsel as soon as the case comes up on his docket.

After entry of this amendment, claims 59-61, 84 (MD), 108, 116, 277-279, 281, 292 (dependent on MD), 294, 298-301, 304 (MD), and 305 (dependent on MD) remain pending, and claims 306-324 are newly presented.

Claim 59 has been amended to strike the label limitation and introduce other limitations.

First, in the preamble, we now state that the kit is for inducing an immune response in a human toward an infectious disease to which a human subject is susceptible, rather than for use to protect a mammal against an infectious disease to which a mammal is susceptible. Hence, we have deleted the language, "at least one of said immunogens acting to protect against said infectious disease when appropriately administered to said subject".

Secondly, the kit is now required at least a single dose of each of **at least two different** immunogens, each capable of inducing an immune response **against the same infectious disease**, and that the kit provide at least two such immunogens **in different amounts**. P33, L9-11 teaches immunization with "multiple immunogens which collectively immunize against the same or different strains for the same infectious disease." And it is recognized that the number of doses (see P25-6, P107) and the amount of a dose (see P51) can vary.

Thirdly, we impose conditions on the specific immunogens included. Specifically, we state that

"at least one of the following conditions holds:

- (1) said kit comprises at least two different capsular pneumococcus immunogens, each conjugated to at least one carrier protein,
- (2) said kit comprises at least two different capsular meningococcus immunogens, each conjugated to at least one carrier protein,
- (3) said kit comprises at least two different acellular pertussis immunogens, or
- (4) said kit comprises at least two different purified viral capsid immunogens"

Capsular immunogens, as in (1) and (2), are contemplated by P35, L14. Acellular pertussis immunogens, as in (3), are contemplated by P43, L6 (it is clear that "acellular" should read as "acellular" because the sentence begins with a reference to "non-whole cell").

The term "viral capsid" is not used as such, but we contemplate "viral" at P34, L3, "membrane" at P35, L15, and "protein" at P34, L18, and the capsid is the protein shell surrounding the genetic material of a virus, and could fairly be referred to as a "membrane". Also, at page 42, line 13, we cite the hepatitis B vaccine of McAleer, USP 4,129,646 (incorporated by reference), and McAleer's "core antigen" is actually a capsid. See Belnap, Diversity of Core Antigen Epitopes of Hepatitis B Virus," Proc. Nat. Acad. Sci. (USA) 100(19): 10884-9 (Sept. 16, 2003) (copy enclosed).

Both meningococcus and pneumococcus are disclosed at P36, L2. Conjugation is disclosed at P43, L5, and also note that P34, L11 teaches combination of agents and P35, L7 teaches tetanus and diphtheria toxoids.

Amended claim 278 requires condition (1), and 277 requires condition (2). New claims 310 and 311 require (3) and (4), respectively.

Finally, we require that the kit is manufactured by a process comprising

accepting at least one lot of at least one immunogen for use in production of the kit after determining a dose of at least one said immunogen is safe according to a method of

a) comparing the incidence, prevalence, frequency or severity of a chronic immune-mediated disorder, or the level of a marker of such a disorder, in a treatment group of humans immunized according to an immunization schedule with one or more doses of said immunogen, with that in a control group of humans,  
and/or

b) comparing the risk of a chronic immune-mediated disorder in a first group of humans immunized according to an immunization schedule with one or more doses of said immunogen, with that in a second group of humans, said first group of humans having been immunized with one or more doses of said immunogen according to a first screened immunization schedule, and the second group of humans having been immunized with one or more doses of said immunogen according to a second screened immunization schedule, each group of humans having been immunized according to a different immunization schedule,

said immunization of (a) or (b) inducing an immune response, comprising production of antibodies or

activation of T-cells, in at least one such group

The comparison steps are based closely on claims in other patents of this patent family. The last clause is introduced to make it clear that a "transformation" occurs.

New claims 306-309 have the scope of former claims 59-62, except that claim 306 omits the reference to animal studies.

New claims 310-315 are dependent on amended claim 59. We have already discussed 310-311. 312 requires that at least one immunogen is genetically engineered, with basis at P34, lines 8 and 10 ("recombinant").

New claims 313-315 require that at least one container comprises at least 3 (313), at least 4 (314) or at least 5 (315) different immunogens. It will be appreciated that since the immunogens are thus in a mixture in the container, any dose drawn from the container will contain all of the immunogens. It is not required that the amounts of the immunogens be equal.

Page 33, lines 9-12 disclose administration of "multiple immunogens which collectively immunize against the same or different strains for the same infectious disease, or multiple immunogens which collectively immunize against a plurality of different infectious diseases."

With regard to multi-strain immunization, there is reference to a three-strain vaccine against polio at page 4, line 27.

With regard to multi-disease immunization, there is reference to a combination of three immunogens (DPT) at page 2, lines 9 and 23-24. There is reference to a combination of four immunogens (DPT + polio) at page 5, lines 7-10.

Further basis is in the schedules of pp. 107-108. Note for example, schedule 4, week 0, wherein administration is

against five different diseases, and schedule 1, week 0, wherein administration is against 10 different diseases.

This must be read in light of the teaching of page 33, lines 15-17 that "the immunogens may be separately or simultaneously administered, and in the latter case, may be combined into a single pharmaceutical for ease of administration."

Claim 316 is directed to kits wherein at least one container is a single dose container.

New claim 317 like amended 59, omits the label limitation of examined 59, and adds a lot acceptance limitation. However, it limits the immunogens as follows: "wherein at least one of said immunogens is an immunogen other than a BCG, diphtheria, pertussis, polio, hepatitis A, hepatitis B, hemophilus influenza, measles, mumps, or rubella immunogen". The basis for this limitation is in original claims 1 and 4. New claims 323 and 324 parallel 84 and 292 respectively.

New claims 318-321 are directed to a method of making a kit. The examiner is reminded that the instant applicant is a PCT national stage application and hence PCT unity rules apply. Thus, claims to the method of making a kit are properly joined with the claims to the kit *per se*.

New claim 322 is directed to a method of making an immunogenic agent.

If claims 318-322 are deemed allowable, applicants would be willing to drop kit claims (some kit claims might be converted into method of making a kit claims).

## **1. Formal Matters**

1.1. The Dec. 12, 2006 restriction was vacated. The present restriction only withdraws from consideration claims 78-83 and 85. This is reflected in the current claims listing.

1.2. On July 1, 2009, Applicants filed a petition for supervisory review of the examiner's refusal to enter and consider the Oct. 18, 2002 declaration (with exhibits) and the Dec. 12, 2002 IDS.

1.3. Claim objections to claims 36, 37, 55, 71, 73, 88, 121, 123, 124, 128, 148, 144, 149, 150, 259, 267, 295, 303 are moot. Claims 267 and 281 have been corrected.

## **2. Indefiniteness Issues**

2.1. Claims 6, 32 (p. 6): This rejection is moot as the claims have been cancelled.

2.2. Claims 8, 10, 11, 16, 32, 34, 35, 38-41, 49-52, 59-65, 86, 96, 97, 100, 102, 109, 118-120 (p. 7): The still pending claims are 59-62. However, claim 59 has been amended to strike the "labeling" limitations, and thus the rejection is moot with respect to it as well as base claims 60-62.

The rejection would presumably be applied to new claims 306-209, which copy former claims 59-62. However, we do not understand the examiner's argument that the labeling limitations are indefinite. We appreciate that it is the examiner's position that these limitations do not satisfy the "functional relationship" test and thus do not serve to distinguish the prior art, but with respect to 35 USC 112 para. 2, the issue is whether the limitation is definite. Certainly, it is within ordinary skill in the art to determine whether the kits include labeling and what that labeling says. Bear in mind that the FDA says what can and cannot be put into the labeling of a pharmaceutical, and those skilled in the art are able to comply with those requirements. The FDA requires that the labeling comprise directions for use, and may require warnings with regard to specific possible adverse effects. Hence, the person skilled

in the art must be able to determine whether the labeling of a particular kit includes instructions for use or warnings, and indeed the specific nature of those instructions and warnings.

2.3. Claims 66-68, 72-74, 117, 126, 150, 266, 267, 278, 279, 295, 98, 299 (p. 7): The examiner questions the distinction between pediatric (defined on p. 35) and non-pediatric (defined on p. 36-37) because the "lists provided for each group are not exhaustive and each group of immunogens/diseases are so varied in etiology, histology, pathogenesis, symptomology and histology, it is determined that the skilled artisan would be unable to distinguish" between them.

As the names "pediatric" and "non-pediatric" imply, the distinction relates to whether these immunogens were customarily administered during childhood. The definition is more precise than that, because immunization patterns vary from one region to another, but that's the basic idea. The alleged variations in etiology, etc. are therefore irrelevant, all that is needed to determine whether a particular immunogen fits the definition of a pediatric immunogen is to inquire into its historical pattern of use. Likewise, there was no need for an exhaustive list of either category of immunogen.

In any event, we have amended the claims to avoid use of these terms.

2.4. Claim 33 (p. 8): This rejection is moot as the claim has been cancelled.

2.5. Claim 36 (p. 9): Moot.

2.6. Claim 87 (p. 9): Moot.

2.7. Claims 27, 32, 33, 36, 56, 103, and 144-148 (p. 9): This rejection is moot as the claims have been cancelled.

2.8 Claim 128 (p. 9): This rejection is moot as the claims have been cancelled.

2.9 Claims 268-276 (p. 10): Moot.

2.10 Claim 280 (p. 10): This rejection is moot as the claim has been cancelled.

2.11. The term "statistically significant" in Claim 281 (p. 10): the examiner says that the requisite comparison teaching to determine whether a degree of association is significant through statistical analysis is not disclosed.

The examiner is mistaken. The importance of statistical analysis is discussed at P63, L14-27. There is specific analysis of statistical significance at e.g., P87, L20-22, and in Tables I-IV.

2.12 Claims 297-303 (p. 11): Moot.

2.13. Claims 300 and 301 (p. 11): The examiner questions the requisite degree for the agent to be considered "substantially free" of immunomodulators other than immunogens (300) or of aluminum salts (301). This is similar to the question asked by the Examiner in In re Mattison, 184 USPQ 485 (CCPA 1975) with respect to the meaning of "substantially increased efficiency". However, the CCPA did not consider "substantially" to be problematic:

We are not persuaded by the board's reasoning that one skilled in the art would not be able to determine the scope of the claimed invention in terms of a specified percentage value. General guidelines are disclosed for a proper



choice of the substituent Ep together with a representative number of examples.... Hypothesizing whether an increase in efficiency of 3%, 30%, or 300% is necessary for said increase to be classified as substantial is not determinative of the issue of whether the claims satisfy 35 U.S.C. 112, second paragraph.

The court reversed the rejection. Clearly, it is not necessary that all quantitative limitations of a claim be expressed as exact numbers.

Applicant discloses compositions in which all of the deliberately incorporated immunomodulators are immunogens, and hence any immunomodulators which are not immunogens would presumably be present in quantities which are not clinically significant. Likewise, Applicant discloses compositions in which aluminum salts were not deliberately incorporated, and the aluminum cation levels in those compositions would presumably be too low to be clinically significant. These are examples of disclosed compositions that would satisfy claims 300 and 301.

P43, L28-P44, L22 addresses the issue of tolerable levels of impurities.

2.14. Claim 302 (p. 11): This rejection is moot as the claim has been cancelled.

### **3. Written Description Issues**

3.1. exclusion of *Streptococcus pneumoniae* (5): moot.

3.2. immunosuppressant (87, 88): moot.

3.3. other than smallpox (106): moot.

3.4. one immunogen can't protect against two different infectious diseases (116): The Examiner is misreading the claim. It says "for use to protect against at least two different infectious diseases, and provides at least one immunogen protecting against **each** of said diseases" (emphasis added). This means that the kit provides at least one immunogen protecting against disease #1, and at least one other immunogen protecting against disease #2. If the claim meant what the examiner thinks it does, the "each of" would be superfluous. However, we have amended 116 to make the intent clearer.

We note that claim 116 does not contradict the "at least two different immunogens ... against the same infectious disease" limitation of amended 59. Claim 59 has a "comprising" transition and therefore the kit may contain additional immunogens. By way of example, a vaccine comprising the oral poliovirus vaccine plus DPT would be providing three different immunogens against the same infectious disease (poliovirus) per amended 59 as well as at least one immunogen against each of four different infectious diseases (poliovirus, diphtheria, pertussis, tetanus).

3.5. exclusion of *Streptococcus pneumoniae* (144): moot.

3.6. Claims 267, 277-279,, 284-291, 294, 295, and 298:  
The examiner says: "While the disclosure briefly mentions that biological immunogens can be carbohydrates on page 35, lines 17-19, there is no explicit or implicit support in the disclosure or the original claims for carbohydrate immunogens or specific meningococcal and pneumococcal carbohydrate immunogens recited in the claims. With regard to conjugation, the only disclosure that can be located is on page 73, lines 25 and 25, but conjugation, or lack of conjugation, is specifically referring to *Hemophilus*

*influenza*. There is no mention in the disclosure of what the *Hemophilus influenza* immunogen is conjugated to. There is also no disclosure that implicitly or explicitly teaches conjugating any immunogen and there is also no mention of carrier proteins, which constitutes new matter."

According to MPEP 2163.02,

"An objective standard for determining compliance with the written description requirement is, "does the description clearly allow persons of ordinary skill in the art to recognize that he or she invented what is claimed." In re Gosteli, 872 F.2d 1008, 1012, 10 USPQ2d 1614, 1618 (Fed. Cir. 1989). Under Vas-Cath, Inc. v. Mahurkar, 935 F.2d 1555, 1563-64, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991), to satisfy the written description requirement, an applicant must convey with reasonable clarity to those skilled in the art that, as of the filing date sought, he or she was in possession of the invention, and that the invention, in that context, is whatever is now claimed. The test for sufficiency of support in a parent application is whether the disclosure of the application relied upon "reasonably conveys to the artisan that the inventor had possession at that time of the later claimed subject matter." Ralston Purina Co. v. Far-Mar-Co., Inc., 772 F.2d 1570, 1575, 227 USPQ 177, 179 (Fed. Cir. 1985) (quoting In re Kaslow, 707 F.2d 1366, 1375, 217 USPQ 1089, 1096 (Fed. Cir. 1983)).

Thus, we must consider not only what is explicitly taught by applicant, but what the person skilled in the art, after reading the specification, would infer had been

conceived by the applicant.

The specification classifies immunogens in a variety of ways: by source (e.g., "bacterial", or more specifically "meningococcal"), by location in the organism (e.g., capsular), and by chemical nature (e.g., carbohydrate).

We respectfully assert that by this kind of systematic analysis, the specification reasonably conveyed that it was applicant's intent to cover the various possible combinations of source, location, and chemical nature, without them having to be laboriously enumerated.

The examiner apparently concedes that applicant conceived of carbohydrate immunogens (support at P34, L10; P35, L18), and conceived of meningococcal and pneumococcal immunogens (P36, L2). Rather, what the examiner questions is whether the inventor had possession of the combination of these concepts, that is of meningococcal carbohydrate and pneumococcal carbohydrate immunogens.

As the examiner is well aware, an immunogen must have some chemical nature; and virtually all immunogens fall within one of the chemical classifications enumerated by applicant. Hence, given that virtually all immunogens are protein, carbohydrate, lipid or a combination thereof (P34, L10-11; P35, L17-19), we think it clear that the skilled worker would infer that the conceived-of meningococcal and pneumococcal immunogens could and would fall in any or all of those categories.

As to the term "conjugated", we agree that the specific reference was to Hemophilus, and that the specification did not state what the immunogen was conjugated to. However, the specification is addressed to the skilled worker. It is routine in the art to refer to an immunogen as being a "conjugated immunogen" when it is composed of antigenic fragments conjugated to an immunogenic carrier.

In this regard, the examiner is reminded that at p. 99-

100, applicants incorporate by reference all patents and articles cited anywhere in the specification. Madore is cited at P6, L4-11 and discloses that the HibTITER vaccine comprises capsular polysaccharide conjugated to the "nontoxic diphtheria toxin variant CRM197." At page 95, lines 23-25, we teach that "FDA approved the Hemophilus influenza polysaccharide vaccine in 1985 and the conjugated vaccine in 1987 (Jama 269: 221-226, 1993)". The latter reference (Adams) states:

A new generation of vaccines with substantially improved immunogenicity was developed in the 1980s by covalently linking (conjugating) PRP with protein antigens. These vaccines included Haemophilus b conjugate vaccine (diphtheria toxoid conjugate) (PRPD); Haemophilus b conjugate vaccine (diphtheria CRM197 protein conjugate) (HbOC), and Haemophilus b conjugate vaccine (meningococcal protein conjugate) PRP-OMP). The conjugate vaccines differ by protein carrier, polysaccharide size, and method of chemical conjugation.

Also, while the cited reference was to Haemophilus, it must be read in the broader context established by the disclosure at P34, L6-14. This refers to "antigens, fragments, or cross-reacting synthetic or recombinantly produced peptides, carbohydrates, lipids or any combination thereof. Such agents can be combined with each other...."

Thus, applicant clearly has a general contemplation of conjugated immunogens, such as an artificial combination of a carbohydrate with a protein. Among the disclosed proteins we have both tetanus and diphtheria toxoid (P35, L7).

3.7. valencies (268-276): moot.

3.8 unique immunological marker (280): moot.

3.9. statistically significant (281): See 2.11 above.

3.10 substance which induces the release of a glucocorticoid hormone (88): moot.

#### **4. Enablement Issues**

4.1. The examiner conceded enablement for claim 266, "since it is only drawn to a pharmaceutical composition comprising immunogenic agents intended to protect against at least one infectious disease". All other examined claims stand rejected for lack of enablement.

4.2. On pages 15-16 the examiner makes various complaints about the claims without explaining their relevance to the issue of enablement.

4.2.1. Thus, the examiner says, "Contrary to 'prophylactic and therapeutic' intent of previously presented claims, new claims 297-303 state that administration... is 'associated with an acceptable risk'.... It is unclear whet a requisite degree of 'acceptable' would be...." This would appear to be a raising an issue of definiteness, rather than one of enablement.

With regard to the propriety of the term "acceptable", we point out that numerous patents have issued that used the claim term "pharmaceutically acceptable". Such claim language plainly contemplates some sort of risk assessment. Moreover, the present specification has a detailed discussion of the issue of acceptability at pages 46-48. Hence, we respectfully submit that the terminology "acceptable risk" is not indefinite.

In any event, the term "acceptable risk" is no longer used in the claims.

Next, the examiner complains about the "pediatric" and "non-pediatric" immunogen terminology; "these are not art-recognized terms ... and the disclosure fails to provide a definition for what is intended by these descriptors." Actually, the specification does define those terms at pages 35-36 and in any event this appears to be an indefiniteness rather than an enablement issue.

The issue is moot since the claims no longer use the pediatric/non-pediatric dichotomy.

Finally, the examiner complains that the method of claim 128 has "no physically active method steps" directed to the goal of "reducing risk of a chronic immune mediated disorder", and characterizes the determination step as a mental process. It appears that the examiner is raising the issue of whether claim 128 should be rejected under 35 USC 101 as non-statutory subject matter.

The issue is moot since claim 128 has been cancelled.

4.3. It is not until p. 17 that any alleged evidence of prima facie non-enablement is presented. The first such "evidence" is the examiner's informal observation that diabetic patients are encouraged to get a flu shot every fall, but that there has been no reported incidence of a reduction in severity after the subjects receive the influenza vaccine. There are so many problems with this argument that it is difficult to decide where to begin.

First, applicant teaches that the timing of the immunization is significant; immunization early in life can reduce the risk of diabetes (P15, L2-7, PL15,L14-P16,L5; P20, L3-10) while immunization late in life can increase it (P16, L6-8; P20, L11-19). The examiner doesn't comment on the age of the patients. Secondly, the number of doses, and the interval between them, can have an effect. (P26, L3-27). The examiner doesn't address that, either. Thirdly, an

effect might be too small to be apparent from clinical anecdotes yet detectable by a well-controlled study of the effect of influenza immunization on diabetic patients. Finally, even if there were no such effect, it does not mean that influenza immunization could not be prophylactic against some form of diabetes.

4.4. Next, we briefly discuss the art cited by the examiner.

Malecki (2008) observes that there are many different types of diabetes. However, there is no showing that the mechanisms resulting in the development of these different forms of diabetes would reasonably be expected to have substantially different sensitivity to immunogens.

Applicant has postulated, in his specification, that interferons modulate diabetes, and that the administration of immunogens affect interferon release by a non-immunogen specific mechanism, as previously discussed in the last Appellant's Brief at pp. 31-33.

Many patents have been issued which claim treatment of a large class of diseases while only showing examples of treating a single disease. In the field of autoimmune diseases, the following patents come to mind:

i) U.S. patent 4,695,459 claim 3 (column 6 line 45) claims a method of treating multiple diseases in humans including multiple sclerosis, systemic lupus erythematosus, psoriasis, juvenile onset diabetes, Sjorgren's disease, thyroid disease, or myasthenia gravis. (These are chronic immune-mediated disorders). The specification only gave an example of treating EAE in mice.

ii) U.S. patent 4,710,380 claim 1 (column 5 line 47) claims a method of treating human or mammal subjects for "disorders characterized by an hyperactive immune response".



The term is similar to the term chronic immune mediated disorders used in our application because both encompasses rheumatoid arthritis, lupus, type I diabetes, and other autoimmune disorders (page 36 line 8). Patent 4, 710,380 contains only examples of rheumatoid arthritis patients being treated with its claimed method, however, its claim 1 encompasses all hyperactive immune responses.

Applicant has shown that early immunization reduces the risk of both diabetes and SLE --two unrelated immune disorders-- in suitable animal models.

Brydak (2000) consider whether immunization of diabetic patients with influenza vaccine was protective, i.e., whether the diabetic state impaired these patients' immune response to the influenza immunogen. Brydak concluded that there was no statistically significant difference in the immune response between the diabetics and healthy controls. Brydak did not examine whether the immunization **affected the diabetes.**

**It should be self-evident that a study that does not evaluate whether an effect occurred is not evidence of the absence of an effect.**

Rizaei [sic, Rezaei] (2008) administered a meningococcus vaccine to children with primary antibody deficiencies. Rezaei's inquiry was into whether these children, with impaired immune systems, would have a protective immune response as determined by antibody titer. Rezaei did not study whether the vaccination had any effect on the risk of CIMD. Moreover, even if Rezaei had reported that there was no effect, it must be remembered that the nexus between immunization and CIMD is necessarily mediated by the immune system, and patients with impaired immune systems could reasonably be expected to be less at risk of vaccine-stimulated CIMD.

Abdullah [sic, El-Madhun] (1998) is similar to Bryzak, i.e., it is looking at the effectiveness of immunization in protecting diabetics against infectious disease (influenza), rather than any side-effect of that immunization on the diabetes.

Gessner (2008) discusses the cost-effectiveness of Hib vaccination in Indonesia, i.e., the **economic** cost of the vaccination (e.g. \$11.74/child for the monovalent vaccine) versus the overall decrease in mortality and disability as a result of vaccine-averted meningitis and pneumonia. No evaluation was made of whether the vaccination would result in any increase in the incidence or severity of any CIMD.

Finn (2002) considers whether the pneumococcal conjugate vaccine should be administered to high-risk children, i.e., those with HIV or SCD (sickle cell disease). Neither of these is within the definition of a CIMD, nor does Finn consider whether the vaccine in question might or might not increase the incidence or severity of a CIMD.

Snape (2008) studied the **immunogenicity** of a tetravalent meningococcal vaccine in infants. While acute side effects were reported, there was no attempt to follow-up and determine whether a chronic immune-mediated disorder such as diabetes developed later in life and whether there was any difference in risk between the 2- and 3-dose schedules, or between the immunized infants and controls.

Harrison (2008)'s abstract states

"Vaccination with self-antigen to promote self-antigen-specific tolerance, 'negative vaccination,' may represent the most specific and potentially safest means of averting automimmune

disease. This strategy is therapeutically effective in inbred rodent models but its translation in humans has failed to meet expectations."

That, apparently, is where the examiner stopped reading the abstract. It continues, more positively,

This failure can be attributed to the use of suboptimal dosage regimens in end-stage disease as well as other factors.... Recent trials of a nasal insulin vaccine in humans at risk of type 1 diabetes provide evidence of tolerance induction as a basis for clinical efficacy.

The cited Table 1 on page 143 is equally unconvincing as evidence of non-enablement. Rather than contending that "negative vaccination" is a chimera, it suggest reasons for failure of human trials of oral tolerance to self-antigens, several of which can surely be overcome (e.g., dosage, bioavailability).

It should further be noted that what applicant is administering is not a self-antigen, but rather an infectious disease-associated antigen.

Zingg (2005) is a German language document with an English language abstract. If the examiner wishes to continue to rely on this document, it is respectfully suggested that the PTO provide a complete English translation, as it is quite possible that there are statements in the body of the article that qualify what is said in the abstract.

So far as can be told from the abstract, Zingg (2005) does not report any new experimental results. Rather, it is

a literature review of sorts. While Classen (2002) is cited as reference (3), it does not appear to cite several of the additional articles which support Classen's findings, such as those cited in the Oct. 18, 2002 declaration. Hence, it does not appear to be a fair review of the literature.

The abstract, at least, merely acknowledges the existence of accusations that vaccinations could cause diabetes, but the instant application teaches that vaccinations can also reduce the risk of diabetes.

Levitsky (2004) does not provide any independent data, but rather relies on the findings of Hviid, see below.

Hviid (2004)'s results were reanalyzed in a peer reviewed paper: Classen, *The Open Pediatric Medicine Journal* 2: 7-10, 2008. This paper showed that in almost every case, the vaccinated group had an higher incidence of diabetes than the unvaccinated group. Hviid's "results" were due to manipulation of the data in a process called "adjusting". HVIID never explained how or justified why he adjusted away the increased risk of diabetes associated with diabetes. Hviid works for a European vaccine manufacturer and has an obvious interest in establishing that his company's products are safe.

PIDJ. In the December 9, 2000 response, Applicant pointed out that the PIDJ article was produced by the Institute for Vaccine Safety IVS) and argued (with supporting exhibits) that the IVS had a vested interest in allaying public concerns that immunization could increase the incidence of diabetes. Response, pp. 16-17.

The PIDJ article says, "no vaccines have been shown to increase the risk of type 1 diabetes in humans". Even if

this statement were taken at face value, it does not address the utility standard under the patent law. The question is where the asserted utility is "credible", not whether it has been proven. Please see the detailed discussion of this legal issue at pp. 34-35 of the last appellant's brief, and the analysis of credibility at pp. 35-85.

**The enablement rejection failed to consider and rebut the pro-enablement art, especially the non-Classen art, set forth in Table 1 of the last Appellant's Brief.**

4.5. The examiner contends that for the claimed kits to be enabled, the kits must perform as specified in the labeling, that is, the art must believe the assertions made in the labeling, i.e., of a nexus between vaccination and CIMD (especially diabetes) such that the choice of immunogen or immunization schedule can increase or decrease the risk of diabetes. Applicants believe, for the reasons explained in the last Appellant's brief, that such a nexus exists, and that the newly cited art does not refute the plausibility of that nexus.

However, the examiner has also taken the position, in making the prior art rejection, that there is no functional relationship between the labeling and the claimed kit, i.e., the meaning of the words of the labeling should be ignored. If so, then it follows that any assertions made in the labeling should be ignored, i.e., all that is necessary to enable the labeling limitations is that it is enabled to print a label and package it with the kit. Which clearly is within the skill in the art.

Hence, we respectfully suggest that there is no present basis for the PTO to doubt enablement of the kit claims with labeling limitations, i.e., present claims 306-309.

If the PTO admits that there is a functional

relationship between the labeling and the kit, and withdraws the prior art rejection, it may at that point make an enablement rejection based on its disagreement as to the believability of the labeling, but not before."

4.6. With respect to present claim 59, this recites that,

the kit is manufactured by a process comprising, for at least one immunogen, accepting at least one lot for use in production of the kit after said immunogen is determined to be safe according to method of

a) comparing the incidence, prevalence, frequency or severity of a chronic immune-mediated disorder, or the level of a marker of such a disorder, in a treatment group of humans immunized according to an immunization schedule with one or more doses of said immunogen, with that in a control group of humans, and/or

b) comparing the risk of a chronic immune-mediated disorder in a first group of humans immunized according to an immunization schedule with one or more doses of said immunogen, with that in a second group of humans, said first group of humans having been immunized with one or more doses of said immunogen according to a first screened immunization schedule, and the second group of humans having been immunized with one or more doses of said immunogen according to a second screened immunization schedule, each group of humans having been immunized according to a different immunization schedule

Thus, Applicant is not now claiming that the immunization reduces or increases the risk of CIMD (including diabetes). It merely requires **testing** for the effect on CIMD. The application clearly teaches how to test for the effect on CIMD.

Moreover, the persons skilled in the art now do test vaccines for their effect on CIMD.

For example, the physician insert for GARDASIL, a Human papilloma virus quadrivalent (types 6, 11, 16 and 18) recombinant vaccine, reported "In the clinical studies, 9-through 26-year-old girls and women were evaluated for new medical conditions that occurred over the course of follow-up. New medical conditions potentially indicative of a systemic autoimmune disorder seen in the group that received GARDASIL or AAHS control or saline placebo are shown in Table 5 (**copy enclosed**).

And for PREVNAR, a 7-valent vaccine in which 7 serotypes of the capsular antigens of Streptococcus pneumoniae were individual conjugated to diphtheria CMR197 protein, the physician insert said, "In a review of all hospitalizations that occurred between October 1995 and August 1999 in the efficacy study for the specific diagnoses of aplastic anemia, autoimmune disease, autoimmune hemolytic anemia, diabetes mellitus, neutropenia, and thrombocytopenia, the numbers of such cases were equal to or less than the expected numbers based on the 1995 Kaiser Vaccine Safety Data Link (VSD) data set." (page 22, copy enclosed).

## **5. Duplicate Claiming**

The examiner object, under 1.75, to claims 27, 59 and 102 as being "substantial duplicates", apparently of each other. While the examiner characterizes this as a double

patenting issue, it is actually considered a definiteness (112 para. 2) "multiplicity" issue, see MPEP 2173.05(n).

The objection as applied is moot as claims 27 and 102 are cancelled and claim 59 amended to no longer have a label limitation. However, we discuss the objection further in view of its possible relevance to claims 306-9. These claims differ with respect to their "label" limitations. As discussed in the section on Prior Art Issues below, the examiner takes the position that the label limitations are properly ignored, whereas applicants take the position that they are properly considered. Since it is clear from the decisions cited on this issue that some printed matter limitations are proper, we believe that applicants have the right to present several claims with different label limitations in the same case, so that on appeal, it can be determined which of these is proper.

The 1.75 objection should be withdrawn unless and until the prior art rejection is upheld on appeal. However, if the examiner believes that the objection is proper at this time, then applicants request that the examiner follow the procedure set forth in MPEP 2173.05(n), i.e., reject the claims under 112 para. 2 for undue multiplicity, so that applicant can take the issue up on appeal.

## **6. Double Patenting Issues (p. 23)**

6.1. The examiner withdrew the double patenting rejection made over USP 5,723,283, on the grounds that the '283 claims were directed to a method of screening, and the then-claimed methods of reducing the incidence or severity of a CIMD or method of protecting mammals from infectious diseases while reducing the risk of a CIMD were distinct.

6.2. Claims 5, 6, 8, 10, 11, 16, 27-30, 32-41, 43, 44, 46, 49-52, 55-57, 59-62, 66-68, 71-74, 77, 84, 90-92, 96-112, 115-128 and 144-152 stand rejected for obviousness-type



double patenting over

- (a) claims 1-10 and 16-42 of USP 5,728,385
- (b) claims 1, 3-7, 10-13, 16, 17, 21, 26, 30, 31, 35, 38-41, 71, 73, and 77-108 of USP 6,638,739.
- (c) claims 1-22, 26-41 and 63-70 of USP 6,420,139.

It is noted that all of the claims still pending are directed to kits, whereas the cited claims of the '385, '739 and '139 patents are directed to therapeutic methods.

A holding of obviousness-type double patenting is improper if the inventions, under US restriction practice, are considered patentably distinct. Compare MPEP 802.01(II) with MPEP 804(II)(B)(1), and see also MPEP 806.<sup>1</sup>

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<sup>1</sup> Indeed, the statute (35 USC 121) provides that if a restriction is made, a divisional application is filed, and the claims of the different applications remain consonant with the restriction, the divisional claims can't be rejected over the parent claims, or vice versa. See MPEP 804.01.

We previously asserted the benefit of 35 USC 121 here because there was a restriction in the parent case between kit and method of use claims, and the May 4, 1999 action section 3 agreed that 35 USC 121 applied. However, the availability of 121 protection is in doubt because this case is a CIP and hence does not meet the statutory definition of a divisional application under *Pfizer v. Teva Pharms. USA*, No. 2007-1271 (Fed. Cir. 2008).

The court overlooked the last sentence of section 121, which implies that a divisional may be a CIP. That sentence reads, "If a divisional application is directed solely to subject matter described and claimed in the original application as filed, the Director may dispense with signing and execution by the inventor. The validity of a patent shall not be questioned for failure of the Director to require the application to be restricted to one invention." If a divisional is always directed "solely to subject matter described in the original application," then this sentence is irrelevant and has no meaning, which is not preferred in statutory construction. At the very least, we should be able to enjoy 121 protection for subject matter in a CIP which is directed to the withdrawn invention of the parent case and supported by the

In the parent case, we received a restriction between the method-of-use claims and the kit claims, i.e., the examiner held that these were two distinct inventions for purposes of both examination and double patenting.

This case is the national stage of a PCT application, hence PCT unity rules determined which claims would be examined. While that meant that both kit and method-of-use claims were examined here, it must be remembered that the PCT unity rules relate to examination procedure, and do not override the substantive national law of patentability. Hence, double patenting determinations should still be based on MPEP Chapter 800, even when the application in question is a PCT application. That is to say, the issue of whether the instant claims are distinct from those of the reference patents is to be adjudicated in accordance with MPEP Chapter 800, without regard to whether the inventions would be considered to have unity under PCT practice.

MPEP 806.05(h) states that a product and a process of using the product are distinct if (A) the process of using as claimed can be practiced with another materially different product; or (B) the product as claimed can be used in a materially different process. Both conditions apply here. Hence, all three double patenting rejections are improper.

6.3. The new method-of-making-a-kit claims are even further removed from the reference patents' therapeutic method claims than are the kit claims per se.

## **7. Prior Art Issues**

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disclosure of the parent case.

In any event, we reserve the right to amend this specification in order to convert it into a divisional application by reverting to the specification of the parent case.

All examined claims stand rejected as anticipated by (a) Madore (1990), (b) Dengrove (1986), (c) Halsey (1985), or (d) John (1984).

7.1. Insofar as the therapeutic method claims are concerned, these rejections have been made and withdrawn before.<sup>2</sup> We not need to dwell on this since the therapeutic method claims have been cancelled for other reasons (primarily to overcome the double patenting rejections), but suffice it to say those claims all had limitations that the PTO has previously conceded avoided anticipation by the cited references, and it's frustrating to have the same rejections come and go and come again.

7.2. With regard to the kit claims, all of these claims previously contained a "label" limitation. However, not only claims 306-309 rely on a label limitation to distinguish the art. These claims will be addressed in section 7.3 below.

7.2.1. As previously noted, all examined claims stand rejected as anticipated by (a) Madore (1990), (b) Dengrove (1986), (c) Halsey (1985), or (d) John (1984).

Claim 59 has been amended, as previously described, and it is believed that the amendments, and in particular clauses (1)-(4), avoid anticipation by the art relied on.

It is the examiner's burden to establish, when rejecting for anticipation, that all features of the claimed

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<sup>2</sup> Pages 16-18 of the March 25, 1999 amendment, explained how the amendments to claim 32 overcame inherent anticipation. The examiner maintained the rejection because he considered the applicable disclaimers to be new matter, and we pointed out that the disclaimers had to be given weight as long as they were in the claim, see p. 6 of the Sept. 7, 2009 after final amendment, citing MPEP 706.03. The advisor action then withdrew at least the rejection of the method claims based on Madore, and any remaining anticipation rejections of these claims were impliedly withdrawn by the action of June 20, 2000.

subject matter are found in a single reference, either explicitly or inherently. If inherency is relied upon, then the inherent feature must flow inescapably from what is explicitly disclosed, it must not merely be possible that the reference possesses the alleged inherent feature.

Madore disclose a monovalent (single strain) Haemophilus influenzae type b conjugate vaccine (HibTITER) in which short-chain oligosaccharides of the Hib capsule are conjugated to the nontoxic diphtheria toxin variant CRM197. All of the oligosaccharides are derived from a single strain of the Hib type, strain Egan, based on evidence from <http://www.wyeth.com/content/showlabeling.asp?id=105>

Hib causes acute bacterial meningitis, and it has a coccal morphology. However, in the art the term "meningococcal" refers strictly to Neisseria meningitidis. Hence, Madore does not satisfy limitation (2) of amended claim 59, and of course Madore does not teach a pneumococcal, acellular pertussis, or viral capsid immunogen.

Halsey discloses monovalent (single strain or single organism) diphtheria, tetanus, pertussis and oral poliomyelitis vaccines, and trivalent (multi-organism) DTP vaccines. It is believed that the pertussis vaccine, and the pertussis component of Halsey's DTP vaccine, is whole cell pertussis, as the art normally identifies vaccines comprising diphtheria, tetanus and acellular pertussis immunogens as "DtaP". It is the examiner's burden to establish that Halsey anticipates the acellular pertussis clause of applicant's amended claim, and this burden has not been met.

Dengrove alludes to the trivalent (multi-pathogen, not merely multi-strain) DTP vaccine consisting of diphtheria, pertussis and tetanus immunogens. Dengrove actually studies just the immune response to diphtheria and tetanus toxoids, i.e., they are made by inactivating the bacterial toxin. To

the extent that Dengrove can be construed as disclosing a DTP vaccine, anticipation is avoided for the reasons discussed in connection with Halsey.

John discloses an oral poliomyelitis vaccine and clearly cannot satisfy any of the numbered conditions of amended claim 59.

7.2.2. New claim 316 requires that "at least one of said immunogens is an immunogen other than a BCG, diphtheria, pertussis, polio, hepatitis A, hepatitis B, hemophilus influenza, measles, mumps, or rubella immunogen" and thus clearly distinguishes Madore, Dengrove, Halsey and John, as they cite no other immunogens.

7.3.3. New claims 317 et seq. are directed to methods of making vaccines, and specifically require that one of the steps be the testing of the immunogens for their effect on the risk of CIMD. No such testing is disclosed or suggested by the cited art, and hence they do not anticipate.

It may interest the examiner to know that in Classen Immunotherapies Inc. v. Biogen IDEC (D. Md., Aug. 16, 2006), see pages 8-9 of the memorandum opinion submitted with the Oct. 5, 2006 IDS, the court denied the motion for summary judgment that the therapeutic method claims of the Classen '139, '739 and '283 patents were anticipated, because there was a genuine issue of material fact as to whether the allegedly anticipatory art taught evaluation of the correlation between immunization and chronic immune-mediated disorders.

7.3. The examiner concedes that "the labeling of the immunogens taught by any of [the references] is not the same as that in the claimed kits...." However, the examiner urges that "Applicant's printed matter is not given patentable weight over the kits and immunogens taught in the prior art, absent some functional relationship between the immunogens

and the label or printed matter," citing MPEP 2112.01 and *In re Gulack*, 703 F.2d 1381, 1385-6, 217 USPQ 401, 404 (Fed. Cir. 1983).

We agree that for the kit claims that still retain a label limitation (claims 306-309), the critical question is indeed whether there is a functional relationship between the immunogens and the label.

What is a "functional relationship"? Presumably, it implies that without the printed matter, the substrate would be **less capable** of performing its function.

In the case of *In re Miller*, 164 USPQ 46 (CCPA 1969), claim 10 read as follows:

A measuring device comprising: a spoon for measuring ingredients; and volume measuring indicia defined in a normal volumetric unit on said spoon of a selected ratio to but indicating a volume different from the actual volume of ingredients being added to and measured in said spoon by said indicia, and a legend attached to said spoon specifying said ratio.

The court's opinion reproduces two apparatus of this type. In Fig. 2, we see a measuring cup with the legend "ONE HALF RECIPE", and various volumetric indicia. The line marked "2 CUPS" actually corresponds to a volume of one cup, so, if a full recipe called for "2 cups", by filling to the line in question, one would actually be adding the amount appropriate for a half recipe. In Fig. 3, we see a set of measuring spoons with a "½ recipe" tag. Here, the spoon marked "1 teaspoon" has a true capacity of ½ teaspoon.

Were these indicia and legends to be removed, one would have cups and spoons worthless for accurate measurement. If just the legends were removed, one would have just a

conventional looking (but inaccurate) measuring device or cup. The Court found that there was "a new and unobvious functional relationship between a measuring receptacle, volumetric indicia thereon indicating volume in a certain ratio to actual volume, and a legend indicating the ratio".

Similarly, in the instant kit claims, there is a new and unobvious relationship among "containers holding pharmaceutically acceptable doses of one or more immunogens" (which is like Miller's "receptacle") the "labeling" of the containers to indicate the identity and amount of each immunogen they contain (which is like Miller's "volumetric indicia")<sup>3</sup> and the "instructions" for use (which is like Miller's "legend").

The last of these points deserves particular emphasis. Miller's "legend" is an instruction for use. "One Half Recipe" is an instruction to the cook to use the cup or spoon as the question when he or she wishes to prepare a "one half" recipe without recomputation of the required amount of each ingredient. Without the cook to interpret the legends and indicia, the cup and spoons do not perform any function. Their functionality resides in what they communicate to the cook. They do not help the receptacle hold more ingredients, or keep them fresher. They do not make the receptacle more watertight or airtight. Their relationship -- especially the legend's relationship -- to the receptacle is closely akin to the relationship exhibited by the printed matter in the instant kit claims to the immunogens of those claims.

In Gulack, the claim was to an educational device, which could take the form of a hat with a headband. Imprinted on the headband (the substrate) was a cyclic sequence of integers (the printed matter) obeying a

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<sup>3</sup> While this is not explicit in claims 27 and 29, it is an FDA requirement. The Supplemental Amendment, if entered, would make this explicit.

particular mathematical rule. What was the functional relationship? According to the CCPA, the digits -- the printed matter -- were "related to the band in two ways: (1) the band supports the digits; and (2) there is an endless sequence of digits... exploit[ing] the endless nature of the band". In contrast, in the prior art Wittcoff reference, there was printed matter on the band, as in (1) above, but the data items were independent rather than arranged in a particular sequence.

Here, the labeling establishes a sequence, albeit temporal rather than spatial, for the use of the immunogens of the kit. Bear in mind that this relationship is between the printed matter and the immunogens, which are a part of the overall "substrate". In Gulack, the distinguishing relationship was between one printed element and another printed element. Hence, the present case actually presents a stronger justification for the finding of a functional relationship than does Gulack.

While the immunogens are functional despite the labeling, that does not mean that a functional relationship is absent. Congress, in enacting the Food, Drug and Cosmetic Act (FDCA), recognized the existence of a functional relationship between a drug and its labeling. Thus, a new drug is not approved per se, rather it is approved for a particular indication (use). The new drug application includes "specimens of the labeling proposed to be used for such drug", see FDCA Sec. 505(b)(1)(F). The FDA reviews the NDA and can refuse to approve if the testing was inadequate to show that "such drug is safe for use under the conditions prescribed, recommended or suggested in the proposed labeling thereof" (see FDCA Sec. 505(d)(1)) or the results "show that such drug is unsafe for use" or "do not show that such drug is safe for use" under "such conditions" (see FDCA Sec. 505(d)(2)). Moreover, approval may be refused if "such labeling is false or misleading in any



particular" (see FDCA Sec. 505(d)(7)).

Once a new drug has been approved, that approval may be withdrawn for the same reasons that approval could have been withheld in the first place. See FDCA Sec. 505(e).

Moreover, the FDCA draws a distinction, for all drugs, between adulteration and misbranding. If a drug contains a substance which is deleterious to health, it is adulterated. See FDCA Sec. 501. However, even a drug free of deleterious substances can be sanctioned if it is misbranded. A drug is misbranded if "its labeling is false and misleading in any particular", see FDCA Sec. 502(a). More significantly, it is misbranded "unless its labeling bears (1) adequate directions for use; and (2) such adequate warning against use in those pathological conditions or by children where its use may be dangerous to health, or against unsafe dosage or methods or duration of administration or application." See FDCA Sec. 502(f). A possible loophole is closed by FDCA Sec. 502(j), which says that a drug is "misbranded" if it is "dangerous to health when used in the dosage manner, or with the frequency or duration prescribed, recommended or suggested in the labeling thereof."

Prescription drugs dispensed by filling the prescription of a physician are exempt from Sec 505(f) and (j), cited above, but only if the drug bears a label presenting "the directions for use and cautionary statement, if any, contained in such prescription." FDCA Sec. 503(b)(2)

According to 21 CFR §201.57(e),

Under this section heading, the labeling shall describe serious adverse reactions and potential safety hazards, limitation in use imposed by them, and steps that should be taken if they occur. The labeling shall be revised to include a warning as soon as there is reasonable evidence of an association of a serious hazard with a drug; a causal relationship need not have been proved.

Plainly, FDA realizes that some manufacturers and their consultants will argue their product has not been proven to cause a serious adverse event even though the data shows an association. FDA requires manufacturers to warn about a potential adverse event as soon as there is any reasonable evidence of an association. This is because it feels that the cost to the public of an unnecessary warning is much less than that of a delayed one.

While a physician may prescribe a drug for an off-label use without violating the FDCA, such prescription may be considered medical malpractice, and insurers may refuse to pay for such use.

We caution the Examiner against an overly restrictive definition of a "functional relationship", namely, that "without the printed indicia or numbers, the substrates lose their function." The case law does not justify that definition.

In Gulack the substrate was a headband. It remained functional as a headband, only its educational function would have been lost if the integer sequence were omitted. In Miller, the substrate was a measuring cup or spoon. It could still be used as a cup or spoon if the indicia were omitted. Thus, it is clear that neither case presented a substrate whose function was totally dependent on the indicia.

Here, it is true that the immunogen (if protective in its own right) could be used to protect against the corresponding infectious disease. However, without the claimed directions for use, the clinician would not know how to use it to limit the increased incidence or severity of the disorder attributable to late immunization.

In determining the functionality of an immunogen, it is appropriate to consider its side effects, not just its specific immunogen effect. If the side effects are

detrimental, its functionality is reduced. If the side effects are beneficial, its functionality is enhanced.

The fact the immunogen has a residual level of functionality, absent the indicia, does not mean that there is no functional relationship between the immunogen and the indicia (labeling). If the latter increases the functionality of the immunogen, the necessary relationship exists and it is proper to give patentable weight to the labeling limitation.

An interpretation of "functional relationship" as meaning necessary for the functioning of the substrate is inconsistent with the alternative holding of the Federal Circuit in In re Lowry, 32 USPQ 2d 1031 (Fed. Cir. 1994). Lowry claimed memory for storing data which comprised a particular data structure (a pyramidal and hierarchical arrangement of "attribute data objects", ADOs), a data processing system comprising a database, a CPU, and memory means for holding the claimed data structure and methods of manipulating ADOs. The Examiner rejected the memory claim under ' 101, the system claims as obvious, and the method claims as anticipated. The Board reversed the ' 101 rejection, and upheld the prior art rejections. According to the Board, Lowry's data structures were analogous to "printed matter" and lacked a "functional relationship" to the substrate (the memory).

On appeal, the Federal Circuit held that because Lowry's data structures upon storage in memory, cause electromagnetic changes, there is a physical change, albeit invisible to the eye, and hence the data structures are not analogous to "printed matter".

However, it continued that even assuming that the analogy is valid, the Board erred in its reliance on Gulack. It pointed out that the ADOs enabled "more efficient data processing operations on stored data" in particular, that they "facilitate addition, deletion and modification of

information stored in memory". The memory, of course, has a "function" even without Lowry's data structure. Lowry's merely structures "provided increased efficiency". However, that qualified as a "functional relationship": "In sum, the ADOs perform a function, Gulack requires no more".

We also think it worth reiterating that if the labeling is given patentable weight (as we think proper as a matter of law), it is clear that the claims are not anticipated or rendered obvious by the reference. While it is certainly normal for an immunogen to be labeled with directions for use, to immunize against an infectious disease, and with warnings of side effects like acute toxicity, applicant was the first to teach that it should be labeled to direct its administration so as to limit the increased incidence and severity of a chronic immune mediated disorder (e.g. diabetes).

Consistent with this analysis, the PTO has allowed claims with "labeling" limitations.

Gerbe, USP 3,627,122, SYSTEM AND APPARATUS FOR THE ADMINISTRATION OF DRUGS (1971), claims an apparatus comprising compartmented trays, with "a patient and dose identification card" covering the bottom of each compartment, the card "having a folded portion...for holding said card in place". The claim also recites that each compartment has "a longitudinal pocket in one wall for a signal identification card".

Phykitt, USP 5,687,841, COMBINATION SHIPPING CONTAINER, MIXING AND DRINKING VESSEL (1997) claims the combination of analgesic medications and a package which serves both a shipping container and a mixing vessel. Claims 21-22 recite

21. The combination, according to claim 1, wherein said package further includes at least one of indications, directions, warnings, drug interaction precautions, active ingredients information and storage information disposed on an outer surface of one of said back portion and

said front portion of said package.

22. The combination, according to claim 21, wherein said package includes each of said indications, said directions, said warnings, said drug interaction precautions, said active ingredients information and said storage information disposed on said outer portion of said back portion of said package.

Robertson, USP 5,752,723, PHARMACY LABEL AND PRESCRIPTION DRUG DISPENSING (1988) claims (18) "a labeled prescription drug package comprising...indicia comprising the name of a prescription drug, the dosage for proper administration of the drug, and the quantity of the drug to be provided in a package, imaged on said first label section".

See also Olney, USP 5,011,853 (claim 18= "a label which indicates that said pharmaceutical agent can be used for reducing the neurotoxicity of at least one cholinergic neurotoxin"); Kelly, USP 5,208,031 (claim 4= "the packaging material indicates that the sexual lubricant mixture... can reduce the risk of being infected by at least one type of sexually transmitted virus"); Sanders USP 4,820,635 (claim 1= "A kit ...comprising... instructions for performing the assay").

While "prior patents" evidence is not conclusive -- it certainly could not justify a legal position which was plainly contrary to the patent statute -- we cannot agree that is legally irrelevant. The courts have repeatedly found such evidence to be probative. Of course, the greater the number of patents cited, the more weight they carry. And the examiner is welcome to attempt to rebut the evidence of showing that a difference in the disclosure justified the difference in prosecution. However, the examiner cannot simply ignore the evidence.

The following cases illustrate the relevance of prior patents:

Ex parte Brian, 118 USPQ 242, 245, (POBA 1958)  
(past practice of office in accepting definiteness  
of "fingerprint" claims);

In re Chakrabary, 596 F.2d 952, 985-86 (CCPA 1979)  
(product claims reciting microorganisms previously  
treated as directed to statutory subject matter);

Andrew Corp. v. Gabriel Electronics, Inc., 6 USPQ  
2010, 2012 (Fed. Cir. 1988) (term "substantially"  
is "ubiquitous" in patent claims and therefore  
considered definite);

In re Cortright, 49 USPQ2d 1464 (Fed. Cir. 1999)  
(Construction of "restore hair growth" for purpose  
of determining both §112 enablement and §101  
utility; prior art references may be indicative of  
how a claim term will be interpreted by those of  
ordinary skill in the art);

Vitronics Corp. v. Conceptronic Inc., 39 USPQ2d  
1573, 1578-9 (Fed. Cir. 1996) (prior art used to  
demonstrate how a disputed term is used by those  
skilled in the art, and indeed is more objective  
and reliable than post-litigation expert opinion  
testimony);

Pioneer Hi-Bred International v. J.E.M. Ag Supply  
Inc., 49 USPQ2d 1813, 1819 (N.D. Iowa 1998)  
(issuance of Boehm USP 2,048,056 in 1936 is  
evidence that "in those instances where inventors  
showed they could define a reproducible plant  
meeting the limits of §112, plant patents were  
issued under §101".)

As for In re Giolito, 188 USPQ 645 (1976) (1976), cited  
by the Examiner in the office action of November 5, 2001,  
page 13, this hardly overrules the numerous post-1976 cases  
which have given weight to prior patents, see above.

The purpose of the patent system is to encourage innovation. The claims are a means of defining the invention in such a manner that it is reasonably clear what has been patented. It is one thing to reject a claim because it covers subject matter which is disclosed or suggested by the prior art, or which is not enabled. It is quite another to reject it on what amounts to stylistic grounds.

The PTO and the courts have recognized the propriety of once exotic claim formats-- "Jepson" claims, "Markush" claims, "product-by-process" claims, "fingerprint" claims, and claims with "negative", "functional", or "alternative" limitations -- because they have realized that public policy demands that inventors not be hindered by hypertechnical claim drafting rules from fully protecting novel, nonobvious, and adequately disclosed inventions.

The instant "kit" claims are a case in point. Applicant has discovered that immunization can --depending on timing - either increase or decrease the incidence or severity of chronic immune-mediated disorders such as diabetes and SLE. A traditional product claim does not sufficiently protect applicant, as it cannot cover a prior art vaccine, even if that vaccine were used without consideration of its effect on a chronic immune-mediated disorder.

For a method claim to protect the invention, it must be crafted to avoid any instance in which the prior art use of a vaccine to immunize against an infectious disease might inherently (although inadvertently) have had the effect of also reducing the incidence or severity of a chronic immune-mediated disorder, as otherwise it could be held invalid on the ground of "inherent anticipation". Applicant has studied the literature, and has attempted to phrase the claim so as to avoid inherent anticipation, but simply cannot be sure that all such art has been avoided. An early

immunization protocol might be set forth in an old or obscure journal anywhere in the world, or might have been used "publicly", without formal publication, in the United States. Indeed, the specification at page 31, lines 9-18 expressly recognizes the problem:

The inventor appreciates that it is conceivable that a prior experimenter has, without recognition of its anti-chronic immune-mediated disorder activity, proposed or even practiced an immunization schedule which falls within the present disclosure. If, under the applicable law, such a proposal or practice would be deemed to anticipate or render obvious an invention here claimed, then it is within the inventor's contemplation to excise from the invention the specific embodiment in question, preserving to the maximum degree permitted by law the scope of protection originally sought.

A second problem with method claim protection is that it is geared to use of immunogens to decrease the incidence or severity of a chronic immune-mediated disorder. However, the Applicant has also enriched the art by teaching it to examine the chronic immune effects of conventional immunization. A vaccine manufacturer may find, after testing inspired by Applicant, that early immunization, while less likely to elicit this adverse effect, is also less effective against the infectious disease, and therefore continue to recommend, with appropriate warnings, late immunization. A "method of reducing the incidence or severity of a chronic immune-mediated disorder" claim would not reach this practice, even though the manufacturer would clearly have benefitted from Applicants's teachings.

A third problem is that the method claims are infringed by physicians. Applicant would prefer to assert direct infringement by the manufacturer. It is easier for Applicant to monitor vaccine labeling than to identify which doctors are following the claimed early immunization strategies.

A "kit" claim, like former claims 27 and 59, solve



these problems, without giving Applicant control of subject matter to which he is not entitled. Former claims 27 and 59 are infringed only if the immunogen is distributed or sold with labeling either giving instructions which call upon the physician to practice the invention, or warnings indicating that the manufacturer has screened the immunogen as taught by Applicant.

Former claims 27 and 59, and present claim 306, could not be inherently anticipated by the naive use of the immunogen in an early immunization schedule, since such use, by definition, would make no reference to the effect of the immunogen on the incidence or severity of a chronic immune-mediated disorder.

Thus, we have explained why the functionality of the immunogens here should be deemed to be affected by the labelling, per Miller and Gulack.

Since the filing of the last appeal brief, a new Federal Circuit decision has come to our attention. In re Ngai, 367 F.3d 1336, 1339, 70 USPQ2d 1862, 1864 (Fed. Cir. 2004) considered both a claim (1) to a method of "normalizing and amplifying an RNA population" and a claim (19) to a kit "comprising instructions describing the method of claim 1 and a premeasured portion of a reagent" selected from a Markush group including "buffers". requiring instructions and a buffer agent.

The Federal Circuit held that the kit claim was anticipated by a prior art reference that taught a kit that included instructions and a buffer agent, even though the content of the instructions differed.

It explained, "Here, addition of a new set of instructions into a known kit does not interrelate with the kit in the same way as the numbers interrelated with the band. In Gulack, the printed matter would not achieve its educational purposes without the band, and the band without

the printed matter would similarly be unable to produce the desired result. Here, the printed matter in no way depends on the kit, and the kit does not depend on the printed matter. All that the printed matter does is teach a new use for an existing product. "

However, the kit in Ngai was used to practice a laboratory method. Here, the kit is one used in therapy, to immunize a patient against an infectious disease. The FDCA requires that the labeling for such a kit provide instructions for use, so that the immunological agents are used in a safe and effective manner. Without the instructions, it is quite unlikely that the practitioner would know how to use the kit to produce the desired result, as immunogens vary in potency and safety.

It does not appear likely that there will be a meeting of minds between applicant and the examiner on the "functional relationship" issue. Consequently, Applicant has minimized the number of "label" claims, and presented new kit and method-of-making-a-kit claims, that avoid the problem in that they do not recite printed matter limitations. Should these claims be acceptable to the examiner, Applicant would be willing to cancel the present "label" claims. Otherwise, it seems likely that the "label" issue will need to be resolved on appeal.

USSN - 08/591,651

Respectfully submitted,

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Enclosures

- PREVNAR physician insert, page 22.
- GARDASIL physician insert, Table 5.
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